REMARKS

Status of the Claims

Claims 47, 58, 59, 61, 67-69, 71-73 and 115-119 are pending in the application. Claims 47, 58, 59, 61, 67-69, 71-73 and 115-119 are rejected. Claim 61 is amended. No new matter is added herein.

Claim Amendments

Claim 61 is amended to correct the claim language and properly depend from independent claim 47. Amended claim 61 limits the method of transducing cancer cells in claim 47 to directly injecting the adenoviral vector among the cancer cells.

The 35 U.S.C. §112, First paragraph , Rejection

Claims 118 and 119 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Applicant respectfully traverses this rejection.

The Examiner argues that although intermediate constructs and sequences are available, it might result in a construct that does not read on the claimed vectors due to variability of the sequence when constructing such a vector. With regards to construction of Adv_{TET}, the Examiner states that the specification teaches that the tet-responsive element and the transactivator element are built into opposite ends of the same vector, but does not provide

information as to specific sequences that are mobilized or into what particular restriction sites the sequences are mobilized, thereby making it unlikely to reproduce the claimed vector without potential sequence variances. With regards to construction of Ad/FasL-GFP$_{TET}$, the Examiner states that although the specification discloses intermediate vectors whose availibility in the future is uncertain, it does not provide details regarding specific sequences or restriction site selections, thereby making it difficult to reproduce the claimed construct.

Applicant respectfully disagrees with the Examiner's contention that the particular vectors of the claimed invention are not enabled by the instant specification. In general, the instant invention provides a regulatable expression vector, for instance, pAd$_{TET}$ that encodes a transactivator protein that binds to a tet-responsive transactivating expression element and a regulatory element comprising a tet-responsive transactivating expression element, where the nucleic acid encoding a protein to be expressed is inserted downstream of the regulatory region (page 5, lines 10-15). More specifically, the instant invention is drawn to Ad/FasL-GFP$_{TET}$ in which the FasL-GFP fusion protein is expressed from TRE promoter. The TRE-controlled FasL-GFP fusion gene and the transactivator element are placed in the opposite ends of the same vector (page 30, lines 1-23). Thus, a novel and inventive aspect of the claimed invention is that the vector is a double recombinant adenoviral vector with the tet-responsive element and the transactivator element built into the opposite ends of the same vector (page 25, lines 14-17, fig. 1C).

With regards to constructing the claimed vectors, the method of constructing fusion proteins and the sequence of murine FasL is known in the art. However, what is important is the length of the FasL that is fused with GFP protein. The instant specification teaches that DNA encoding 11 to 279 amino acids of the murine FasL was placed downstream of the GFP sequence present in a commercially available vector. The instant specification further teaches that all the vectors used to construct the claimed vectors were commercially available. Hence, the maps of these vectors are also known. The specification and the figures of the instant invention provide further guidance as to the arrangement of the genes in the vector with reference to the restriction sites and the length of the gene sequence within the vector (page 26, lines 16-26; Figs. 1A-1C). Since construction of vectors is routine in the art, Applicant contends that based on the guidance provided in the specification and figures, one of ordinary skill in the art will be able to construct an adenoviral vector with the tet-responsive element and the transactivator element built into the opposite ends of the same vector.

Applicant also respectfully disagrees with the Examiner's contention that since there is no assurance that the intermediate vectors will be readily available for the entire term of the issued patent, the claimed vectors cannot be reproduced. Applicant submits that uncertainity in the availability of the intermediate vectors does not preclude the specification from enabling the instant invention. Since the maps of these intermediate vectors are available, one of ordinary skill in the art can easily construct the intermediate vectors using the common molecular biology techniques known in the art. Further, one can use the

teachings of the instant invention to arrive at the claimed vectors. Hence, Applicant contends that the instant specification provides ample guidance to one of ordinary skill in the art to arrive at the claimed vectors. Accordingly, based on the above-mentioned remarks, Applicant respectfully requests that the rejection of claims 118 and 119 under 35 U.S.C §112, first paragraph be withdrawn.

Claims 47, 58-59, 61, 67-69, 71-73 and 115-119 stand rejected under 35 U.S.C. §112, first paragraph, for lack of enablement for *in vivo* use. Applicant respectfully traverses this rejection.

The Examiner has maintained the rejection of these claims since Applicant's arguments made in response to this rejection in the last Office Action were found unpersuasive. In response to Applicant's argument regarding the use of tissue specific or inducible promoter for regulated expression to enable efficient delivery to target cells and uniform regulation of FasL expression, the Examiner states that there is unpredictability regarding the delivery and not regarding regulated expression of a protein.

With regards to Examiner's statement regarding unpredictability in delivering the vector to target cells, Applicant submits that the instant specification teaches a method of treating a tumor containing cells that express Fas by introducing a nucleic acid encoding a Fas ligand (FasL) into a second tumor cell using the vector described *supra*, whereby this second tumor cell expresses FasL and interacts with the Fas^+ tumor cell to cause the apoptosis of the Fas^+ cell (page 6, line 29-page 7, line 5). The instant specification further teaches the

bystander effect induced by the claimed method in prostatic adenocarcinoma where these prostate cancer cells undergo apoptosis through a paracrine/autocrine mechanism (Example 3). Thus, the instant invention teaches a method of gene therapy that obviates the need to infect every cell within the tumor. Further, the inclusion of tissue specific promoters limits the expression of the therapeutic gene to tumor cells and the inducible promoters modulate timing and duration of the gene expression in these cells. The instant specification teaches construction of adenoviral vectors using tissue-specific promoters with inducible promoters to allow parenteral delivery of the virus for treating metastatic disease (page 35, lines 2-4). In fact, systemic delivery of such a vector in mice was observed to be safe at doses that were lethal for FasL-GFP vector with CMV promoter (see enclosed abstract: Mol. Ther. 2001, 4(5): 416-426). Thus, based on the above discussion, the claimed method not only ensures that all the cells within that tumor undergo apoptosis but that the apoptotic effect will be localized to the tumor and not affect surrounding normal cells.

Further, to point out unpredictability in the art, the Examiner cites **Arai** *et al* where although the vector was localized to tumor mass, inflammation was observed in abdominal muscle layer beneath the injection point. Furthermore, in response to Applicant's argument regarding tumor immune privilege where the Applicant asserts that the immune death is localized since the vectors are localized in cancer cells, the Examiner argues that since the claim reads on a vector being administered through any means, the vector and FasL expression is not limited to a particular locus. Additionally, if the vector is administered directly

into the tumor, then there is unpredictability with regards to immunotoxicity (inflammation).

With regards to unpredictability in the state-of-the-art for performing cancer gene therapy in general, Applicant contends that cancer gene therapy is not static and has progressed significantly over the years (Abstract, *Future Oncology*, 2005, 1(1): 115-123). Although there have been some difficulties associated with somatic cell gene therapy in the past, overall there have been no reported results of any sort that indicate that cancer gene therapy is going to result in the adverse effects. With regards to Examiner's statement of teaching of inflammation in the abdominal muscle layer in **Arai** *et al.* as a reason for unpredicatbility in the art, Applicant would like to respectfully point out that the same art teaches that no significant histological changes were observed in the major organs of treated mice because FasL expression was localized at the injection site and expression at the distant organs were lower (page 3866, col. I, parag. II). Thus, although inflammation was observed at the site of injection, it did not result in any toxic effect.

Applicant respectfully disagrees with Examiner's statement regarding tumor immune privilege. The prior art cited by the Examiner (Nat Med., 1999, 5(3):267-268) teaches that anti-tumor response involving FasL could be hindered by FasL's ability to suppress anti-allograft response or by FasL's ability to induce inflammmatory response. Applicant would like to respectfully point out the instant specification does not disclose any immune cell death as is observed during allograft rejection. In fact, the instant specification teaches that the claimed

virus could be administered without lethality and resulted in tumor cell growth retardation *in vivo* (page 37, lines 3-11). With this in mind, Applicant submits that the purpose of including a tissue specific promoter and an inducible promoter in a vector is to limit the expression of a gene to specific target cells as discussed *supra*. Hence, systemic administration of the claimed vector will limit the expression of FasL to a particular locus i.e. tumor cells. Thus, any immune cell death will be localized to the tumor tissue and not have a systemic effect. Additionally, Applicant contends that if adminstration of viruses did promote an inflammatory response at the site of tumor, this would be beneficial to the *in vivo* use of the claimed viruses since the tumor burden would be reduced by both apoptotic induction by FasL itself and by the immune cells recruited to the inflammatory site.

Further, with regard to immunotoxicity when the vector is administered directly into tumor, Applicant submits that the toxic effect of the vector will be restricted to the tumor and not be systemic. For instance, the vector used in **Arai** *et al.*, did not comprise a tissue specific or a inducible promoter. Nevertheless, the inflammatory response induced by this vector of **Arai** et al. was localized to the site of injection and did not affect the major organs as discussed *supra*. Compared to this vector, the claimed vector of the instant invention has tissue specific which would limit the expression of FasL to particular locus and eliminate the systemic toxic effect of the vector. Despite this, should the virus leak out of the tumor and a systemic toxic effect is detected, the instant

specification teaches of shutting off the virus by either downregulating or upregulating the inducible promoter (page 37, lines 15-27).

With regards to Applicant's submission of Exhibit A as evidence to use the invention *in vivo*, the Examiner argues that an immunocompetent model would not address the issues of immunotoxicity or immunoneutralization whereas an immunocompromised model would not address the issues of unpredictability of FasL expression in non-target cells or delivery of FasL to unintended cells/tissue.

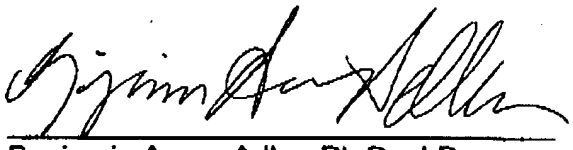
Applicant submits that the claimed vector of the instant invention was injected directly into tumors implanted in nude mice (page 37, lines 3-11; Example 4; enclosed Declaration) or administered systemically (see abstract: Mol. Ther. 2001, 4(5): 416-426) and observed to have therapeutic potential and no lethal effects. With regards to unpredictability with regards to expression of FasL in non-target cells or delivery of FasL to unintended cells/tissue, Applicant has already discussed this issue *supra* with reference to the tissue specific and inducible promoters in the vector. Overall, Applicant contends that the claimed invention provides ample guidance for one skilled in the art to practice the invention *in vivo*. Accordingly, based on the above-mentioned remarks, Applicant respectfully requests the withdrawal of rejection of claims 47, 58-59, 61, 67-69, 71-73 and 115-119 under 35 U.S.C. 112, first paragraph.

This is intended to be a complete response to the Final Office Action mailed May 17, 2005. Applicants submit that the pending claims are in condition for allowance. If any issues remain outstanding, please telephone the undersigned attorney of record for immediate resolution. Applicant also encloses a

petition to extend the time for filing this response for one (1) month to and including September 19, 2005. Please charge the $60 extension fee to the credit card identified on the enclosed PTO-2038. In the absence of this form, please debit the fees due from Deposit Account No. 07-1185 on which Applicant's counsel is allowed to draw.

Respectfully submitted,

Date: 8/25/05



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